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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
GABEL,G	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 08/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/382,622	Dess et al.
Examiner	**Group Art Unit**
Gailene R. Gabel	1641

☒ Responsive to communication(s) filed on *Aug 25, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-30, 51, and 52* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-30, 51, and 52* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3-5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

1. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application in the first sentence of the specification (37 CFR 1.78).

Drawings

2. The drawings in this application are objected to by the Draftsperson (see PTO-948 attached). Correction is required. However, formal correction of noted defect can be deferred until application is allowed by the examiner.

Specification

3. The abstract of the disclosure is objected to because it does not sufficiently describe the disclosure. Furthermore, the abstract of disclosure is replete with grammatical errors. Correction is required. See MPEP § 608.01(b). Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text

for details. The language should be clear and concise and should not repeat information given in the title.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2-30 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites improper Markush language in reciting "selected from the group comprising". See also claims 3, 8, 9, 11, 19, 22, 27, and 29.

Regarding claim 2, the phrase "and its derivatives" renders the claims indefinite because the claim includes elements not actually disclosed (those encompassed by "and its derivatives"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d). See also claims 3 and 9.

Claim 4 recites improper and overlapping Markush language in reciting "selected from the group comprising ... or".

Regarding claim 4, the phrase " including those containing aldehydes, ketones, alcohols..." renders the claim indefinite because the claim includes elements not actually

disclosed (those encompassed by "including those containing"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 4 is indefinite in reciting "DNA and RNA". Acronyms or abbreviations must be recited at least one time in a set of claims.

Regarding claim 4, the phrase "or other hydrophilic or hydrophobic moieties" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "or other"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 6 is indefinite in reciting "CAT scan". Acronyms or abbreviations must be recited at least one time in a set of claims.

The term "large content" in claim 8 is a relative and subjective term that renders the claim indefinite. The term "large content" is not defined by the claim, the specification does not provide a standard for ascertaining their requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 11 is fails to recite positive limitation in reciting "said vehicle being selected from the group".

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. In this case, it is unclear what structural cooperative relationship exists between "diseased tissue" in claim 12 and

"biologically sensitive structures" and "cellular membranes" in the instant claim and all subsequent claims that make reference thereto. See claims 13-17, 21, 23-24, and 28. For example, is the "biologically sensitive structure" the same as or a part of "the diseased tissue".

Claim 12 is indefinite and unclear in reciting "a preference for" since the term "preference" is a subjective term which lacks comparative basis for defining its metes and bounds. See also claim 13.

Claim 12 is indefinite and unclear in reciting "biologically sensitive structures" since the term "biologically sensitive" is subjective and lacks comparative basis for defining its metes and bounds. See also claims 14, 15, 16, 17, 21, 23, 24, and 28.

Claims 14 and 15 are indefinite and unclear in reciting "biologically targets" and "chemically targets said biologically sensitive structures" because it is unclear how each mode of "targeting" is effected in relation to claims 16, 17, and 18.

Claims 16 and 17 lack antecedent support in reciting "said targeting".

Accordingly, claim 16 is confusing in reciting "said targeting is by chemical partitioning of the agent" because it is dependent upon claim 14 which recites "biologically targets...".

Regarding claim 19, the phrase "or its derivatives" renders the claims indefinite because the claim includes elements not actually disclosed (those encompassed by "or its derivatives"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 21 lacks antecedent support in reciting "said targeting".

Claim 21 is indefinite and unclear in reciting "physically" since the term "physically" is a subjective term which lacks comparative basis for defining its metes and bounds. See also claims 22, 28, and 29.

Claim 23 lacks antecedent support in reciting "said targeting".

Claim 24 lacks antecedent support in reciting "said targeting".

Claim 28 lacks antecedent support in reciting "said targeting".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-30 and 51-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diseased tissue such as cancer and tumor cell tissues, does not reasonably provide enablement for treatment of any diseased tissue such as parasitized and infected muscle tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in *In re Wands,* 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of the experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the

nature of the invention, the state of prior art, the relative skill of those in the art, and the breadth of the claims.

As to the diseased tissue, the direction and guidance in the specification is notably limited to *specific* neoplastic tissue, such as cancer tissue and tumors. While this is sufficient guidance and direction for treatment of neoplastic tissue, wherein radiosensitizer agents are introduced and concentrate preferentially into such tissue to allow increased dose of ionizing radiation for treatment, it does not teach or suggest how to treat alternative diseased tissue such as infected tissue and pathologically enlarged cardiac muscle tissue, etc. Based on this limited disclosure and direction, one of the skill in the art would not know how to detect alternative diseased tissue, using the instant halogenated xanthene radiosensitizer agent, without undue experimentation.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 5-8, 10, 12-13, 15-16, 23, 28-30, and 51 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975).

Serafini et al. teach a radiosensitizer agent for use in treating diseased tissue (radiopharmaceutical agent). Specifically, Serafini et al. teach halogenated or iodinated rose bengal which is principally tetrachlorotetraiodofluorescein, that allows for rapid and efficient incorporation into molecules resulting to overall reduction in imaging time and radiation

exposure together with improved images (see Abstract). In a study, Serafini et al. intravenously injected iodinated Rose Bengal into healthy volunteers, then blood clearance studies were performed in addition to urinary clearance and simultaneous and sequential scintiphotos were taken of the cardiac, liver, biliary, and intestinal systems. Sufficient concentration into diseased tissue (localization) within the liver then the rest of the biliary tree of the radiopharmaceutical agent is observed with marked improvement in anatomic detail showing specific areas of radioactive concentrations (see page 630, column 2).

7. Claims 1-3, 5-10, 12-13, 15-16, 23, 28-30, and 51 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)).

Neckers teaches a radiosensitizer agent: Rose Bengal or 2,4,5,7- tetraiodo-3', 4', 5', 6'-tetrachlorofluorescein, which has the spectral, photochemical, and photophysical properties of a halogenated xanthene. Neckers teaches that Rose Bengal, disodium salt is characterized by (1) large absorption in all solvents, (2) capacity as imaging agent (shows fluorescence), (3) its triplet is completely quenched by oxygen, (4) concentration on selected tissues, i.e. tumor (its spectrum is most diagnostic of its immediate environment), (5) it bleaches in protic, polar solvents, (6) is a photodynamic sensitizer, (7) its singlet may be quenched by strong oxidizing agents (see page 1). The absorption and emission spectra of known Rose Bengal derivatives are enumerated in Table 2 and 3, respectively. In conclusion, Neckers teaches the halogenated xanthene, Rose Bengal,

whose characteristic increased absorptivity, fluorescence, and specific diagnostic concentration on specific spectrum provides inherent capability to be sensitized or activated using X-rays and other ionizing radiation in order to treat diseased tissue, in addition to its current use as imaging agent when exposed to such ionizing radiation.

8. Claims 12-17, 21-24, 28-29 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Norman et al., Invest Radiol, 26: S120-S121 (1991).

Norman et al. teach a radiosensitizer agent (iodinated contrast media/ gandolinium) for treatment of diseased tissue using radiosensitization or ionizing radiation wherein doses absorbed from diagnostic X-rays are enhanced. Norman et al. specifically teach that the radiosensitizer agent exhibits preference to (help localize) biologically sensitive diseased tumor tissues. In experimentation, Norman et al. showed that survival of rabbits increased when irradiation therapy was preceded by injection (infusion) of the iodinated contrast media (see page S120, column 1, paragraph 1). Norman et al. further teach that the dose enhancement factor (DEF) which increases linearly with the concentration of iodine can also be achieved with conventional administration of contrast media (S120, column 1 and 2). Figure 1 shows a plot of the DEF as a function of the iodine concentration in a lymphocyte medium during irradiation at 140 kVp. In conclusion, the therapeutic ratio, the ratio of radiation dose absorbed by a diseased brain tumor tissue versus that absorbed by the surrounding normal brain tissues increases with increasing iodinated contrast media in the diseased tissue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 18 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norman et al. (Invest Radiol, 26: S120-S121, 1991) in view of Khaw et al. (US 5,780,052).

Norman et al. have been discussed supra. Norman et al. fail to teach encapsulating the radiosensitizer agent for delivery into diseased cancer tumor.

Khaw et al. disclose a method of enhancing effects of therapy that kills diseased (malignant/tumor) cells in vivo by providing (immuno)liposomes specific for an internal cellular antigen present in degenerating neoplastic cells. Techniques are known for liposome targeting such as conjugating antibodies to cell-surface (malignant) antigens to pharmacologically active agents and labels to permit diagnosis, localization, and therapy toward tumors (see column 7, line 48 to column 8, line 3). The liposomes contain antineoplastic agent for initiating therapy in a mammal to kill malignant cells in vivo (see column 2, last paragraph). The antineoplastic agents include radiosensitizing agents, cytotoxic agents, and radionuclides (see column 3, first paragraph and column 4, lines 18-27). In diagnostic procedures, (immuno)liposomes containing radiosensitizer and diagnostic agent which are specific for intracellular antigens, i.e. a detectable molecule such as an imaging agent are injected into a patient receiving radiation therapy.

Following administration, an imaging technique is employed such as computed axial tomography (CAT) scan and X-ray imaging (see column 16, line 18 to column 17, lines 3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the radiosensitizer agent taught by Norman using liposomal targeting mode of infusion as taught by Khaw because Khaw specifically taught that antineoplastic agents such as radiosensitizer agents can be incorporated into liposomes for use in initiating therapy in animals to kill malignant tumors in vivo and such liposome targeting methods containing pharmacologically active agents and labels allow diagnosis, localization, and therapy directly toward specific tissues. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teachings of Norman into the method of Khaw because of the multifunctional capacity as achieved in combining treatment and imaging capability using a single radiosensitization agent for treatment of cancer or tumorous tissues.

10. Claims 4, 11, 14, 17-22, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Khaw et al. (US 5,780,052).

Serafini et al. and Neckers have been discussed supra.

Serafini et al. and Neckers fail to teach encapsulating the halogenated xanthene, Rose Bengal, for delivery into diseased cancer tumor.

Khaw et al. has been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer halogenated xanthene taught by Serafini et al. or Neckers using liposomal targeting mode of infusion as taught by Khaw because Khaw specifically taught that antineoplastic agents such as halogenated xanthenes can be incorporated into liposomes for use in initiating therapy in animals to kill malignant tumors in vivo and such liposome targeting methods containing pharmacologically active agents and labels allow diagnosis, localization, and therapy directly toward specific tissues. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teachings of Serafini or Neckers into the method of Khaw because of the multifunctional capacity as achieved in combining treatment and imaging capability using a single radiosensitization agent for treatment of cancer or tumorous tissues.

11. No claims are allowed.

Remarks

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Sharma discloses a method for vectored delivery of physiologically active chemical agents to target organ, tissue, or cell of interest, including rose bengal as a vectoring agent.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

G Gabel 8/24/00

Gail Gabel
Patent Examiner
Group 1641

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